A Journal of the Gesellschaft Deutscher Chemiker

Angewandte International Edition GDCh Chemie

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Accepted Article

Title: TBD-Enhanced Activity of Peroxide Intermediates in Phosphine-Free α-Hydroxylation of Ketones

Authors: Yongtao Wang, Rui Lu, Jia Yao, and Haoran Li

To be cited as: *Angew. Chem. Int. Ed.* 10.1002/anie.202014478

Link to VoR: https://doi.org/10.1002/anie.202014478

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10.1002/anie.202014478

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RESEARCH ARTICLE

1,5,7-Triazabicyclo[4.4.0]dec-5-ene Enhances Activity of Peroxide Intermediates in Phosphine-Free α-Hydroxylation of Ketones

Yongtao Wang, Rui Lu, Jia Yao, Haoran Li*

[*] Dr. Y. Wang, R. Lu, Dr. J. Yao, Prof. Dr. H. Li
Department of Chemistry and ZJU-NHU United R&D Center
Zhejiang University
38 Zheda Road, Hangzhou, 310027, P. R. China
E-mail: lihr@zju.edu.cn
Prof. Dr. H. Li
State Key Laboratory of Chemical Engineering and College of Chemical and Biological Engineering
Zhejiang University
38 Zheda Road, Hangzhou, 310027, P. R. China

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Abstract: The critical role of double hydrogen bonds was addressed for the aerobic α-hydroxylation of ketones catalyzed by 1,5,7-triazabicyclo[4.4.0]dec-5-ene (TBD), in absence of either metal catalyst or phosphine reductant. Experimental and theoretical investigations were carried out to study the mechanism. In addition to initiating the reaction by proton abstraction, a more important role of TBD was revealed to enhance the oxidizing ability of peroxide intermediates, allowing DMSO an efficient substitute of commonly used phosphine reductants. Further characterizations with the nuclear Overhauser effect spectroscopy (NOESY) confirmed the double hydrogen bonds between TBD and ketone, and kinetic studies suggested the attack of dioxygen on the TBD-enol adduct to be the rate-determining step. This work uncovered the enhancing role of TBD on the oxidizing ability of peroxides, and should encourage the application of TBD as a catalyst for oxidations.

Introduction

The selective C-H bond oxidation by dioxygen has been pursued for a long time.[1] As an oxygenation product of the α-C(sp^3)-H bond, the α-hydroxy-carbonyl group commonly exists in natural products and bioactive molecules,[2] and shows potential usages as the photoinitiator and the privileged synthon.[3] Although it is the most sustainable and green oxidant, dioxygen is difficult to react directly with C-H bond.[4] The aerobic oxygenation of α-C(sp^3)-H bond in ketones was mostly initiated by bases, with excess phosphine reductants added for high selectivity. Ritter group reported a highly efficient binuclear palladium catalyst for aerobic α-hydroxylation of carbonyl compounds,[5] and introduced 1,5,7-triazabicyclo[4.4.0]dec-5-ene (TBD) as both ligand and additive. Schoenebeck and coworkers achieved the aerobic oxidation of ketones in DMSO using Cu_2O catalyst along with stoichiometry TBD,[6] and they uncovered the detailed C−C cleavage mechanism as well as substrate-dependent selectivity. Instead of transition-metal catalysts, Jiao group developed a highly efficient method, in which Cs_2CO_3 was used as catalyst.[7] Besides, 2 equiv $P(OEt)_3$ was added to reduce the peroxide intermediate. More recently, Gnanaprakasam et al. also developed a transition-metal-free method,[8] avoiding the use of phosphine reductant by introducing stoichiometry KO^{t}Bu. Besides, Zhao and coworkers fulfilled the enantioselective α-hydroxylation using the phase-transfer catalysts with aqueous KOH as well as phosphine reductant.[9] The use of stoichiometry base or phosphine reductant is required in above mentioned methods, thus a more green catalysis system is of interest to oxidize the α-C(sp^3)-H bond in ketones.

Mechanistically (Figure 1), it is commonly accepted that the hydroxylation is initiated by proton abstraction, and both carbanion[7-8] and enol[9] have been proposed as the intermediate, which then react with dioxygen to form peroxide intermediate. Phosphine reductant was generally used for reducing the peroxide intermediate,[7] otherwise this intermediate would form the carboxylic acid byproduct via C−C cleavage.[6] However, when studying the hydroxylation of ketones in DMSO, we found that catalytic amount of TBD could lead to a high yield, and the loading of Cu_2O catalyst had no beneficial effect (Figure S1). The green and efficient aerobic hydroxylation under the metal- and phosphine-free condition encouraged us to investigate the catalytic role of TBD.

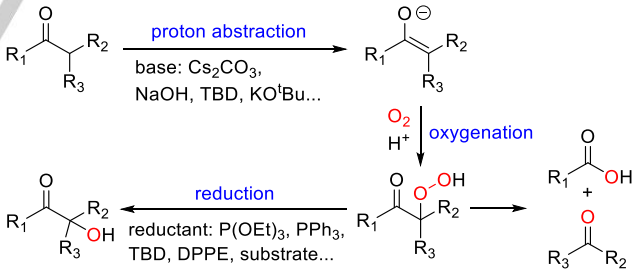

Figure 1. Previously proposed mechanism for aerobic hydroxylation of carbonyl compounds.

Though TBD has been introduced in the hydroxylation of ketones, its role is still not clear. Ritter and coworkers found that TBD was not solely a base,[5] because the replacement of TBD by 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) or 7-methyl-1,5,7-triazabicyclo-[4.4.0]dec-5-ene (MTBD) led to poor performance. Schoenebeck and co-workers suggested that the TBD worked as both base and reductant,[6] thus they used stoichiometry TBD in their system. Due to lack of detailed investigations, the controversy still remains over the role of TBD. Besides, TBD has been widely used as the catalyst in many reactions owing to its special structure,[10] especially in addition reactions and ring-

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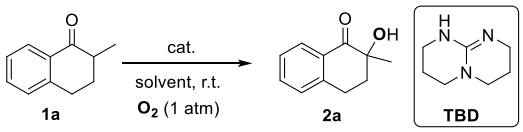
opening polymerizations.[11] In these reactions, the double hydrogen bonds were proposed for the TBD promoted proton transfer.[12] Recently, Dale and coworkers reported the control of regioselectivity for N-alkylation by TBD.[13] The tightly combined TBD-triazole adduct through double hydrogen bonds was determined with X-ray diffraction as well as the diffusion-ordered ^{1}H NMR spectroscopy (DOSY).

Herein, we report the TBD-catalyzed aerobic α-hydroxylation of ketones in free of either metal catalysts or phosphine reductants. DMSO as the solvent was revealed to reduce the peroxide intermediates toward hydroxylated products. The role of TBD and detailed mechanism were investigated by means of control experiments, isotropic labeling experiments, kinetic studies, ^{1}H-NMR, the nuclear Overhauser effect spectroscopy (NOESY), combined with computational calculations. As a result, the dual catalytic role of TBD via doubly proton transfer process was revealed, uncovering the TBD-enhanced activity of peroxide.

Results and Discussion

Reaction development and influencing factor examination

Table 1. Effects of different parameters on the oxidation of **1a** using dioxygen[a].

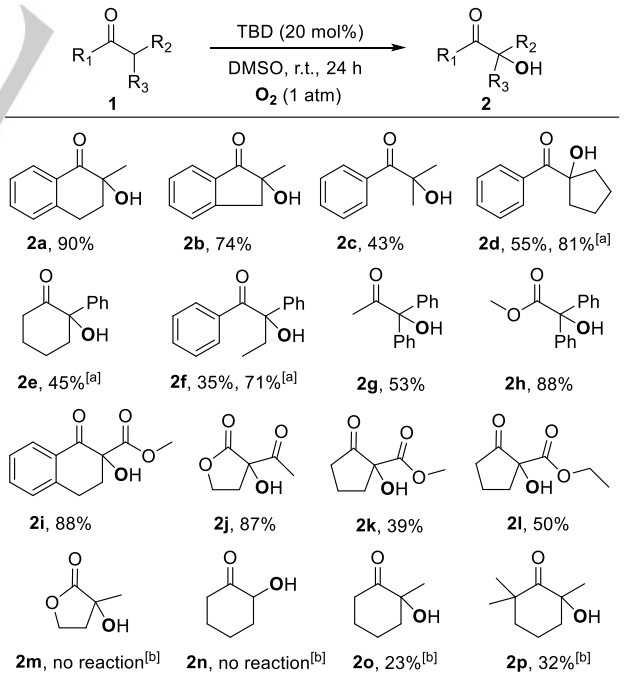


Entry	Cat. (equiv)	Solvent	Time [h]	Conv. [%]	Yield [%]
1	TBD (**1.0**)	DMSO	2	100	97
2	TBD (**0.8**)	DMSO	2	100	96
3	TBD (**0.6**)	DMSO	5	100	94
4	TBD (**0.4**)	DMSO	5	100	92
5	TBD (**0.2**)	DMSO	12	100	93
6	TBD (0.2)	**Toluene**	12	8	3
7	TBD (0.2)	**THF**	12	5	1
8	TBD (0.2)	***n*-Butanol**	12	11	2
9	TBD (0.2)	**1,4-dioxane**	12	8	1
10	TBD (0.2)	**DMA**	12	24	11
11	TBD (0.2)	**DMF**	12	50	14
12	**K_2CO_3** (0.2)	DMSO	12	N.R.	0
13	**DBU** (0.2)	DMSO	12	11	3
14	**Cs_2CO_3** (0.2)	DMSO	12	10	2

[a] Conditions: substrate (0.5 mmol), catalyst (0.1-0.5 mmol), solvent (2 mL); the reaction was performed at room temperature with 1 atm O_2. The conversion and yield were determined using gas chromatography (GC) with biphenyl as the internal standard. [b] The value in parentheses was the catalyst loading in equivalent.

When processing the TBD participated aerobic hydroxylation of 2-methyl-1-tetralone (**1a**) in DMSO, we found the use of metal catalyst or phosphine reductant was not necessary (Figure S1). Even the TBD loading could be as low as catalytic amounts. Tsang et al. considered TBD both a base and the reductant for the peroxide intermediate,[6] and they used 1.1 equiv TBD in place of phosphine reductant in the Cu_2O-Catalyzed hydroxylation. During our study, to our delight, as the TBD loading was reduced from 100 mol% to 20 mol% (Table 1, entries 1-5), comparable yield of **2a** was obtained (from 97% to 93%), despite the decrease of reaction rate. It is reasonable that catalytic amounts of TBD can initiate this reaction via proton abstraction, however, the confusing issue is how the peroxide intermediate is reduced to **2a** in absence of phosphine reductant.

Firstly, we investigated the influencing factors. Several solvents were utilized in place of DMSO to evaluate the solvent effect (Table 1, entries 6-11), but none of them performed better. The reactions in toluene, THF, butanol and 1,4-dioxane occurred in much low conversion and yield for hydroxylation, while **2a** was in yield of only 11% in DMA and 14% in DMF. Considering different types of bases as catalysts (Table 1, entries 12-14), we found K_2CO_3 was not basic enough to initiate the reaction, while the selectivity was too low with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) (27%) and Cs_2CO_3 (20%), though they should be basic enough. The byproduct of this reaction has been detected to be carboxylic acid,[6] by which the basic catalyst could be passivated during the reaction. Therefore, the low conversion with DBU and Cs_2CO_3 should be caused by the low selectivity. Consequently, using DMSO as the solvent and TBD as the catalyst is required to gain high selectivity for hydroxylation, which should depend on the competition between C−C cleavage and reduction of the peroxide intermediate.



Scheme 1. Scope of TBD-catalyzed hydroxylation. The yield was obtained for isolated product under standard conditions (Table 1, entry 5). [a] 50 mol% TBD was used. [b] The reactions were detected using ^{1}H NMR with 1,3,5-trimethyoxybenzene as internal standard.

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Under the optimized condition, the reaction scope was examined (Scheme 1). The secondary α-carbon at cyclohexanone (**1n**) was found inactive, while **1o** and **1p** with tertiary α-carbon could yield hydroxylated products, **2o** and **2p**. The ester **1m** did not react in this condition, but substitutions at α-carbon with carbonyl or phenyl could activate esters, leading to acceptable yields (**2h-2l**). Therefore, the reactivity of ketones should be affected by the acidity of α-proton, then activating groups like phenyl and carbonyl at α-site would benefit this reaction. Moreover, cycloketones were found to generate more hydroxylated products than the chain ketones (**2b vs. 2d**). Though the phenyl group at **1e** made it reactive, only 45% **2e** was obtained even in use of 50 mol% TBD, thus, a low selectivity could be supposed for **2e**. We will return to explain these different reactivities and selectivities later, after mechanism investigations.

Identifying the reductant for peroxide intermediates

It has been proved that the peroxide intermediate was formed during the aerobic hydroxylation of carbonyl compounds.[8, 14] Generally, this intermediate is reduced efficiently by phosphine reductants such as $P(OEt)_3$ and PPh_3.[7, 9] Considering no phosphine reductant used but comparable yield obtained in this work, next, we focus on determining whether there is another species playing the role to reduce peroxide intermediates.

By monitoring the reaction of **1a** with gas chromatography (GC), we found that dimethyl sulfone ($DMSO_2$) arose along with the production of **2a** (Figure S3-4). The generation of $DMSO_2$ allowed us to suppose DMSO as the reductant to convert the peroxide intermediate to **2a**. In order to test whether DMSO participated in the hydroxylation, we related the consumed dioxygen (detected using a communicating vessel, Figure S2) as well as the produced $DMSO_2$ with the reacted substrate. As shown in Figure 2, equivalent dioxygen was consumed along with the reaction of **1a** (Figure 2, black, y = 1.04x - 0.012), and equivalently generated $DMSO_2$ (Figure 2, red, y = 0.096x – 0.105). These correlations verified the participation of DMSO in the hydroxylation of **1a** as the reductant. The other evidence was attained from the ^{18}O-labelling experiments (Scheme 2a). When ^{18}O-labeled dioxygen was used to oxidize **1a**, both the hydroxylated product **2a** and $DMSO_2$ were found to be incorporated by one ^{18}O atom, characterized by GC-MS (Figure S5). On the basis of above results, both quantitative studies and ^{18}O-labelling experiments supported our previous conjecture that DMSO was the oxygen acceptor of the peroxide intermediate.

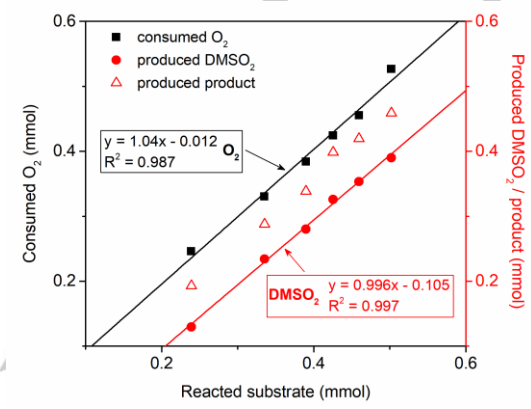
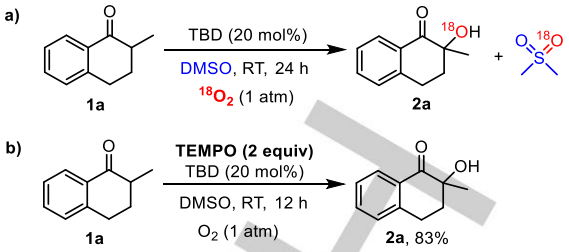


Figure 2. The relationship between the reacted substrate and the consumed dioxygen (■), produced $DMSO_2$ (●) or formed product (Δ).



Scheme 2. (a) Reaction of **1a** with ^{18}O-labeled dioxygen. (b) Reaction of **1a** in presence of 2.0 equiv TEMPO as the radical inhibitor.

Considering the ionic mechanism has been proposed for the hydroxylation of ketones,[1a] we also suggested the ionic mechanism for the hydroxylation of **1a** in this work, where DMSO played the role as reductant. The 2.0 equiv TEMPO was added at the beginning of the reaction to inhibit possible radical routes, however, no apparent decrease of the yield was observed after full conversion (83% vs. 93%, Scheme 2b). Because the reaction not inhibited by TEMPO was found inhibited by 3,5-di-tert-4-butylhydroxytoluene (BHT),[15] and the acidic phenol will inactivate the basic TBD in our conditions, we could only propose this ionic mechanism, but could not absolutely confirm.

TBD-enhanced activity of peroxide intermediates

Though DMSO has been revealed as the reductant, the reaction catalyzed by Cs_2CO_3 in place of TBD could not occur in comparable selectivity (Table 1, entry 14). Using phosphine reductant, however, Liang and Jiao have proved Cs_2CO_3 an efficient catalyst for the hydroxylation of ketones.[7] Thus, the alkalinity of Cs_2CO_3 alone was strong enough to initiate the reaction, and the other function of TBD except alkalinity should be required for the reduction of peroxide by DMSO. As a support, the addition of Cs_2CO_3 into TBD/DMSO system apparently accelerated the reaction (Table 2, entries 1-2), improving the conversion from 69% to 100% at 2 h, with similar selectivity (90% vs. 91%).

In light of the unique efficiency of TBD for the high selectivity, we evaluated the effect of structure characteristic on its catalytic role. The methylation of the amino group in TBD results in another guanidine, 7-methyl-1,5,7-triazabicyclo-[4.4.0]dec-5-ene (MTBD), which has the similar pK_{BH+} value (25.4 in MeCN) as that of TBD (26.0 in MeCN).[16] Taking MTBD in place of TBD, however, the reaction gave much lower conversion (12%), and did not afford hydroxylated product in acceptable selectivity, not even with the addition of Cs_2CO_3 (Table 2, entries 3-4). Thus, the amino group is crucial for the catalytic role of TBD.

Bicyclic guanidines, including TBD, MTBD and DBU, have been commonly used as the strong organic base,[10-11, 11c, 17] where TBD showed much higher activity for the reactions involving proton transfer, like Michael reactions,[11b] or ring-opening polymerization of lactones.[11e, 18] The high performance of TBD was suggested to be caused by its unique structural characteristic,[10, 12] which allowed the double proton transfer via forming double hydrogen bonds. Moreover, during the N-alkylation of triazoles, the double hydrogen bonds between TBD and triazole lead to the high regioselectivity.[13] Therefore, in our reactions, we surmised that the double proton transfer was involved in the TBD-catalyzed reduction of peroxide intermediates.

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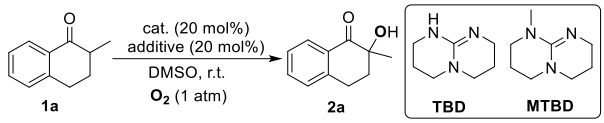
Table 2. Control experiments[a].



Entry	Cat.	Additive	Time [h]	Conv. [%]	Sele. [%]
1	TBD	none	2	69	91
2	TBD	Cs_2CO_3 (20 mol%)	2	100	90
3	MTBD	none	12	12	33
4	MTBD	Cs_2CO_3 (20 mol%)	2	15	33

[a] The conversion and selectivity were determined using GC with biphenyl as the internal standard.

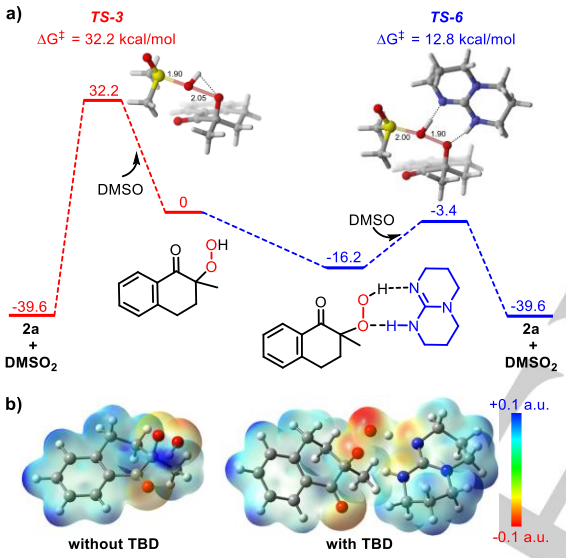


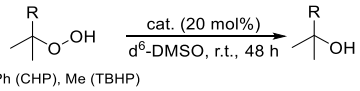
Figure 3. (a) Gibbs free energy profile for reduction of the peroxide intermediate by DMSO, with (blue) and without (red) TBD. (b) The electrostatic potential (ESP) on the 0.01 au isodensity surface of the peroxide intermediate without (left) and with (right) TBD linked (C: grey, H: white, N: blue, O: red).

We carried out DFT calculations to evaluate the influence of double hydrogen bonds on the peroxide reduction, where the key step is the formation of S-O bond. By searching the transition state (Figure 3a, ***TS-3***), we found the formation of S-O bond was along with the breaking of O-O bond, accompanied by proton transfer, generating **2a**. In absence of TBD, this step was forbidden, with activation free energy as high as 32.2 kcal/mol. Driving by the double hydrogen bonds, the peroxide intermediate thermodynamically tended to combine with TBD (ΔG = -16.2 kcal/mol), and then its reaction with DMSO (through ***TS-6***) was 19.4 kcal/mol favored, resulting in a passible activation free energy, 12.8 kcal/mol. Moreover, the charge distribution at peroxide might account for the catalytic activity of TBD. Figure 3b illustrates the electrostatic potential (ESP) of the peroxide intermediate without and with TBD linked. According to color range, we can find that the negative potential at the peroxide oxygen was apparently enhanced by TBD. With more negative charge at oxygen, the peroxide was motivated to attack the positively charged sulfur atom at DMSO. As a result, the TBD-enhanced activity of peroxide allowed its reaction with DMSO. Though the double proton transfer has been reported in TBD-catalyzed reactions,[12, 19] to the best of our knowledge, its application on enhancing the reactivity of peroxide has not been uncovered yet.

Afterward, we used two commercially available peroxides, cumene hydroperoxide (CHP) and *tert*-butyl-hydroperoxide (TBHP), to react with d^6-DMSO, in the hope of verifying the catalytic activity of TBD on the reduction of peroxides. With ^{1}H-NMR spectra, the yield was determined based on the peak area of methyl group (Table 3, also see Figure S6). Stirring CHP in d^6-DMSO for 48 h, little CHP was reduced, producing 2% 2-Ph-2-propanol (entry 1). To our delight, when 20 mol% TBD was used, CHP fully conversed to 2-Ph-2-propanol (entry 2). Meanwhile, the generation of $DMSO_2$ was confirmed by GC-MS (Figure S7). Under the same condition, but with MTBD in place of TBD, only 19% 2-Ph-2-propanol was obtained. The higher efficiency of TBD than MTBD was also observed for the reaction of TBHP (entries 4-5, Figure S8), where 39% and 4% *tert*-butanol was produced under the catalysis of TBD and MTBD, respectively. Due to the wide applications of CHP and TBHP as oxidants, the enhancement of their oxidizing ability by TBD may help improving their reactivity or broadening their applications.

^{1}H-NMR experiments supported the proposed mechanism for the promoting effect of TBD on peroxide reduction. Figure 4 illustrates the change of ^{1}H-NMR spectra during the TBD-catalyzed reduction of CHP in d^6-DMSO. The signals in dashed box are 40-fold decreased, belonging to the methyl group at CHP (star-labeled) or that at 2-Ph-2-propanol (spade-labeled). In addition, when TBD was added into the solution of CHP in d^6-DMSO, the peak for exchangeable proton at CHP shifted upfield from 11.0 toward 6.6 ppm, suggesting the proton exchange or the existence of hydrogen bonds between TBD and CHP. Combining with the results of theoretical study, we supposed that TBD interacted with CHP through the double hydrogen bonds, enhancing the oxidizing ability of CHP, then the doubly proton transfer made the reaction between CHP and DMSO passable. As CHP was reduced to 2-Ph-2-propanol, the peak of the exchangeable proton continued shifting upfield toward 4.3 ppm. Consequently, the catalytic role of TBD was confirmed for the reduction of peroxides, where the doubly proton transfer process was suggested.

Table 3. Reduction of peroxides in d^6-DMSO[a].



R = Ph (CHP), Me (TBHP)

Entry	Sub.	Cat.	Time [h]	Yield [%]
1	CHP	none	48	2
2	CHP	TBD	48	100
3	CHP	MTBD	48	19
4	TBHP	TBD	48	39
5	TBHP	MTBD	48	4

[a] The yield was determined in use of ^{1}H-NMR.

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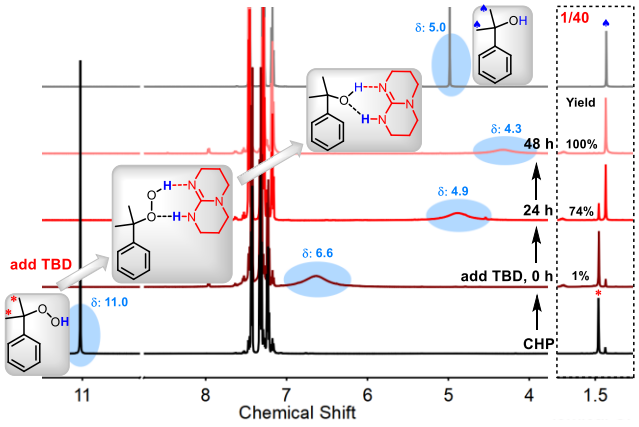

Figure 4. ^{1}H-NMR spectra for the reduction of CHP in DMSO. Signals in the dashed box are 40-fold decreased, and the chemical shift was given in ppm.

Mechanistic studies on the aerobic C-H oxygenation

The above studies revealed mechanistic insights into the reduction of peroxide intermediate, which determines the selectivity for hydroxylation. Following, we focus on the reactivity of ketones toward dioxygen. The triplet dioxygen is thermodynamically unfavorable to react with the α-C-H bond at ketones.[4] Without metal catalyst to activate dioxygen, in this reaction, carbanion should be formed via α-proton abstraction with the help of basic catalyst, then readily reacts with dioxygen. Several groups have reported the excellent ability of TBD for proton abstracting,[11b-e, 18-20] and the doubly proton transfer mechanism was also proposed. With much effort, we observed the interaction between ketone and TBD in use of NMR, then kinetic experiments and theoretical calculations were carried out to investigate the rate-determining step.

To characterize the interaction between TBD and **1a**, we concerned the ^{1}H NMR signal of amine group at TBD (Figure 5a). In absence of ketones, the 0.25 M TBD in d^6-DMSO showed a broad peak at 4.83 ppm, belonging to the exchangeable proton of its amine group. Adding 0.5 and 1.0 equiv **1a** to this solution at N_2 atmosphere, the chemical shift of this signal shifted from 4.83 to 5.07 and 5.29 ppm, respectively. According to the reported relationship between chemical shift and hydrogen bond strength,[21] such downfield peak shift ($\Delta\delta$ = 0.46 ppm) should suggest the formation of hydrogen bond between TBD and **1a**.

Moreover, when two protons are spatially close, the dipolar cross-relaxation can be detected by the two-dimensional nuclear Overhauser effect spectroscopy (2D NOESY).[22] With this method, hopefully, the combination of TBD and ketone might be identified through the cross peak between protons. To avoid the influence of signal interference (Figure S9), we took **1b** in place of **1a** for NOESY analyses, and characterized the equivalently mixed TBD with **1b** in d^6-DMSO under N_2 atmosphere (Figure 5b). According to the heteronuclear Overhauser effect spectroscopy (HOESY, Figure S10), the signal belonging is signed at the side ^{1}H NMR spectra, and the expanded peak is given for the exchangeable proton at TBD, along with that in absence of **1b**. As expected, cross peaks were observed between the exchangeable proton at TBD (H_a) and the α-proton at **1a** (H_c), confirming the hydrogen-bonded **1a** with TBD. To our delight, the H_c was also found spatially correlated with the methylene proton at TBD (H_d). The observation of H_c-H_d and H_a-H_d correlations could be attributed to the existence of double hydrogen bonds, for their spatially close range. Moreover, the thermodynamic preference of the double hydrogen bonds was also verified by DFT calculations, discussed later.

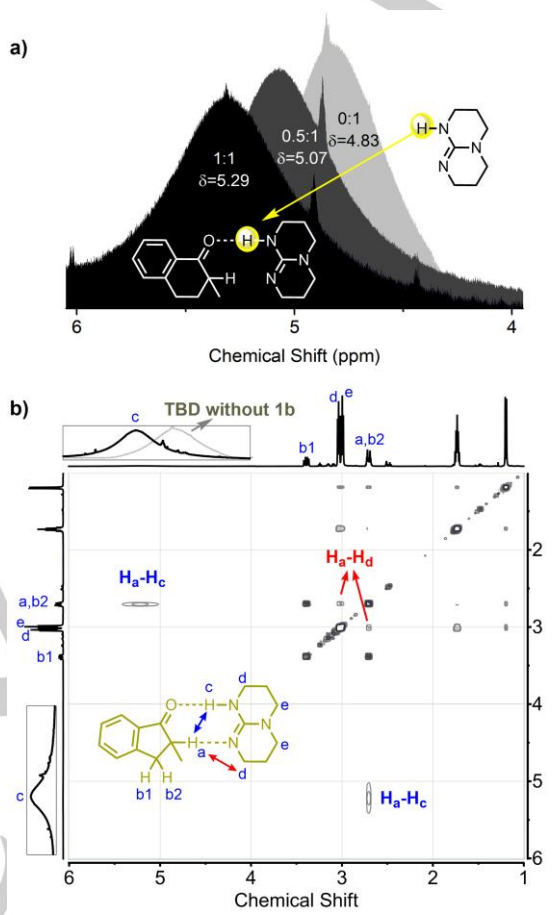

Figure 5. (a) ^{1}H NMR spectra of the exchangeable proton at TBD in d^6-DMSO (0.25 M), with addition of 0, 0.5, and 1 equiv **1a**. (b) The symmetrized H,H-NOESY spectrum of the equivalently mixed **1b** and TBD in d^6-DMSO (0.25 M). The enlarged signal of the exchangeable proton at TBD was given along with that in absence of **1b** (grey).

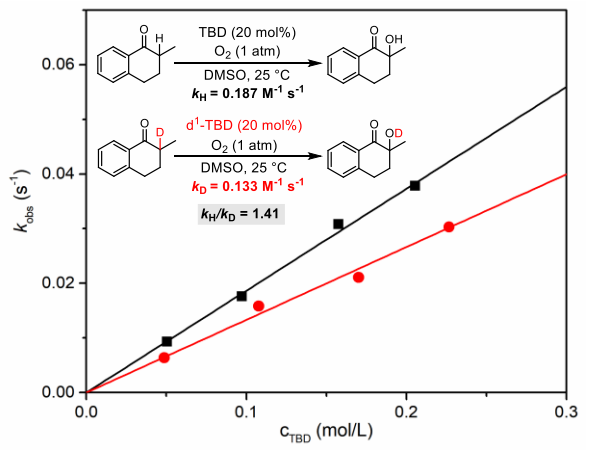

Figure 6. The relationship between k_{obs} and the concentrations of TBD without (■) or with (●) hydrogen deuterated, for determining the second-order rate constants and k_H/k_D.

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Further kinetic experiments were conducted to explore the rate-determining step. By monitoring the reaction with GC, we found the concentration of **1a** followed the exponential decay (Figure S11), indicating a first-order kinetic for the reaction of **1a**. Besides, by detecting the observed rate constant (k_{obs}) with different amounts of TBD, we found the reaction also followed a first-order kinetic for TBD (Figure 6, black). Fitting with the linear function, a second order rate constant (k_2) of 0.187 M^{-1} s^{-1} was obtained. Such results indicate the equivalently participating of ketone and TBD in the rate-determining step. In addition, when the α-proton at **1a** and the exchangeable proton at TBD were deuterated (Figure S12), the reaction rate was decelerated, with k_2 = 0.133 M^{-1} s^{-1} (Figure 3, red). Accordingly, the KIE was calculated to be 1.41, much lower than the commonly observed primary isotope effect, belonging to the secondary isotope effect.[23] Therefore, the rate-determining step of this reaction could not be the C-H bond breaking, then was proposed to be the attack of dioxygen on the TBD-combined enol intermediate, with O-H bond involved.

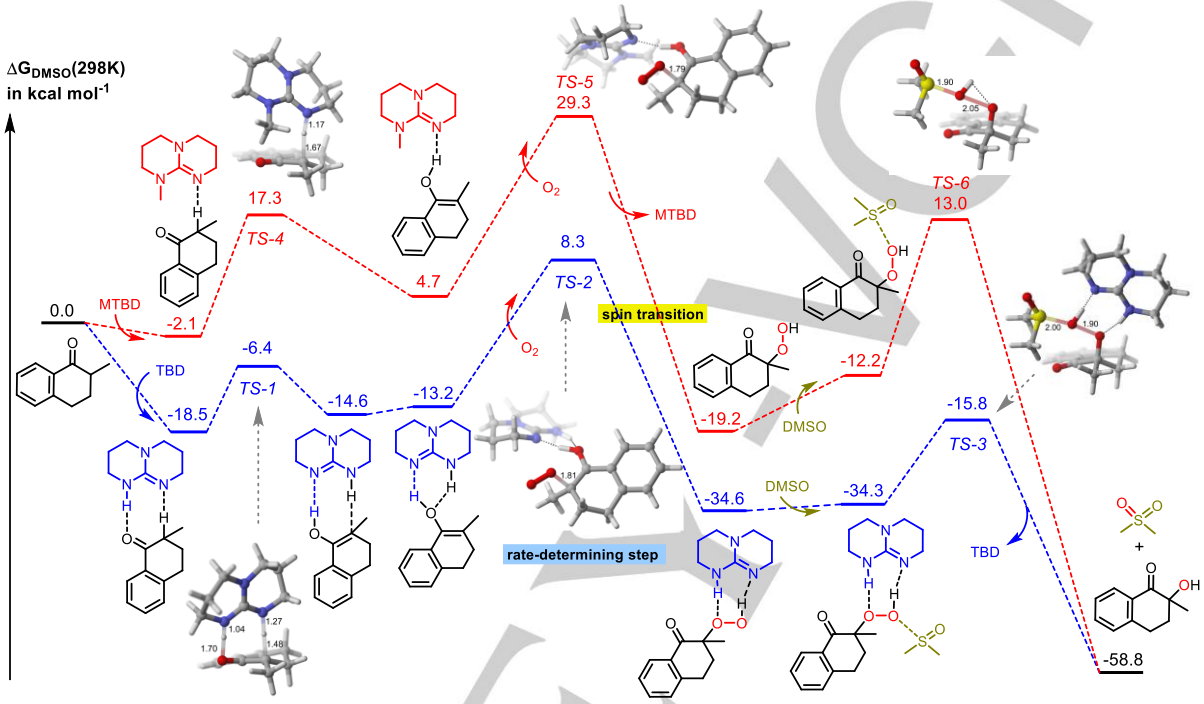

Figure 7. Gibbs free energy profile for hydroxylation of **1a** catalyzed by TBD (blue) or MTBD (red). The free energies (with DMSO solvation) are given in kcal/mol. (C: grey, H: white, N: blue, O: red). Distances are shown in angstrom.

As illustrated in Figure 7, DFT calculations were carried out for the hydroxylation of **1a** catalyzed by TBD (blue) and MTBD (red). Benefitting from the double hydrogen bonds, the former was apparently favorable in Gibbs free energy. The doubly proton-transfer process (through ***TS-1***) was 7.3 kcal/mol favored than that of the one proton-transfer process (through ***TS-4***), and generated the TBD-enol adduct with double hydrogen bonds kept. Being slightly endothermic (3.9 kcal/mol), the α-proton transfer for the substrate was reversible. Here the stabilization of enol by TBD was quite important to the whole reaction, because it lead to a much lower thermodynamic penalty from ketone to enol, which has been found to be about 10 kcal/mol and was one of the key kinetic obstacles for this type of transformation.[24] After another endothermic process (1.4 kcal/mol), there formed an enol intermediate with TBD combined at the O-H group. The attack of triplet dioxygen on the enol intermediate should go through a spin transition process. Thus, we performed a MECP (minimum energy crossing point) calculation to find the singlet-triplet crossing point, and obtained a structure with lower energy than that of the triplet transition state. Thus, the Gibbs free energy barrier was calculated to be 22.9 kcal/mol. As a result, the C-O bond formation served as the rate-determining step. Accordingly, it is reasonable that the first-order kinetic was found for both **1a** and TBD. The formation of C-O bond was accompanied by the O-H bond breaking, leaving TBD-H^+ to combine with the -OO^- group, forming the TBD-associated peroxide intermediate.

As to the MTBD catalyzed pathway, both substrate activating and peroxide reduction were slowed down, especially, the reduction of peroxide intermediate by DMSO turned to be the rate-determining step and was impassable (32.2 kcal/mol). Therefore, the carboxylic acid should be generated during the MTBD catalyzed pathway, and would inactive the catalyst by the neutralization reaction, leading to low conversion. Consequently, the DFT studies reinforced a consistent mechanism with that suggested by the experimental results.

Proposed catalytic cycle

According to the above discussed studies on the mechanism, we proposed the catalytic cycle for the TBD catalyzed oxidation of ketones (Figure 6). Firstly, TBD combines with ketone through the double hydrogen bonds. Then the α-proton was abstracted by the imide group at TBD, accompanying with the proton transferring from the amino group at TBD to the carbonyl oxygen. The synergistic doubly proton-transfer process promoted the α-proton transferring, and generated a double hydrogen bonds stabilized enol with TBD. After the breaking of the N-H group from

α-site sp^2-carbon, the attack of dioxygen on the enol was the rate-determining step, leading to the formation of peroxide intermediate. Most importantly, TBD enhances the oxidizing ability of peroxide intermediate via the double hydrogen bonds, allowing its reaction with DMSO. The hydroxylated product was generated after the reduction, while the DMSO was oxidized to $DMSO_2$. Moreover, suggested by Schoenebeck et al.,[6] the unreduced peroxide would proceed the C-C cleavage to produce carboxylic acid and ketone as the byproducts. In this mechanism, TBD played the dual catalytic role in both substrate activation and peroxide reduction, via the doubly proton-transfer process.

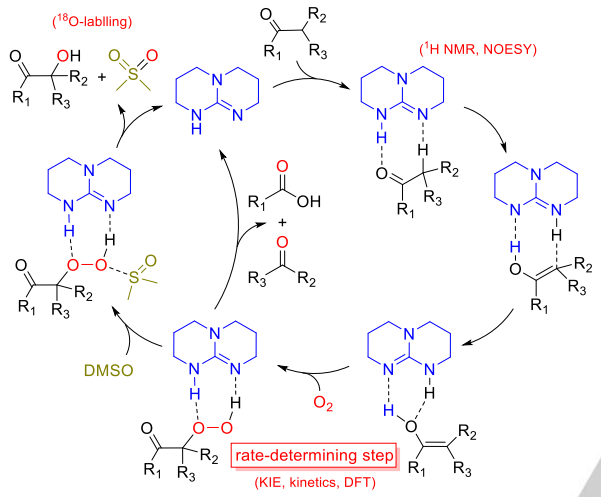

Figure 8. Proposed catalytic cycle for TBD-promoted hydroxylation of ketones.

Consequently, reactivity of ketones should be affected by the endothermic transformation from ketones to enols, because this thermodynamic penalty will be added to each kinetic barrier afterwards. In order to explain the reason for unreactive **1m** and **1n**, we calculated the Gibbs free energy change for enolization (ΔG_1) of ketones (Table S2). ΔG_1 values for **1n** (6.0 kcal/mol) and **1m** (18.0 kcal/mol) were significantly higher than that of **1a** (3.9 kcal/mol), causing reasonable inactivity of **1n** and **1m**. The acylation of **1m** at α-carbon resulted in a sharp decreased ΔG_1 from 18.0 to -10.2 kcal/mol, which was in agree with the high reactivity of **1j**. Moreover, the methylation and phenylation of **1n** reduce ΔG_1 to 4.9 and 3.0 kcal/mol, leading to more and more reactivity. The low selectivity for **1e** could be explained by the reactivity of its peroxide intermediate to form dioxetane, which turned to byproduct after C-C cleavage.[6] We calculated the Gibbs free energy change from peroxide intermediate to dioxetane (ΔG_2, Table S2), and found ΔG_2 of **1e** (8.7 kcal/mol) was much lower than the values for **1a** (13.1 kcal/mol), **1o** (13.0 kcal/mol) and **1j** (12.9 kcal/mol). Accordingly, easier formation of dioxetane made the peroxide intermediate for **1e** generate more carboxylic acid, and less **2e**.

Conclusion

In summary, the dual catalytic role of TBD via doubly proton transfer process was described for the phosphine-free α-hydroxylation of ketones. The first role of TBD is to activate ketones via proton abstraction, where the double hydrogen bonds between TBD and ketones were characterized with both 1D ^{1}H NMR and 2D NOESY. The role for proton abstraction depends on the alkalinity, and is replaceable by other bases like MTBD or Cs_2CO_3. Most importantly, the second but critical role of TBD is to catalyze the reduction of peroxide intermediates, which determines the selectivity. The formation of double hydrogen bonds between peroxide and TBD results in an enhanced activity of peroxide, allowing its reduction by DMSO toward the hydroxylated product. As a support, the catalytic role of TBD on the reduction of CHP and TBHP by d^6-DMSO was confirmed. Accordingly, the dual catalytic role of TBD enabled a green strategy for aerobic oxygenation of C-H bonds, avoiding the usage of either metal catalyst or hazardous stoichiometric phosphine reductant. Considering the remarkable effect of TBD to enhance the oxidizing ability of peroxides, we anticipate this work to be a starting point in applications of TBD into oxidation reactions where the peroxide plays the role as oxidant or intermediate.

Acknowledgements

The authors gratefully thank Prof. Dr. Shengming Ma for helpful discussions, and gratefully thank Mrs. Ling He for the nuclear Overhauser effect spectroscopy (NOESY). This work was supported by the Fundamental Research Funds for the Central Universities, and the National Natural Science Foundation of China (No. 22073081).

Keywords: double hydrogen bonds • aerobic hydroxylation • guanidine • peroxide • reaction mechanism

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10.1002/anie.202014478

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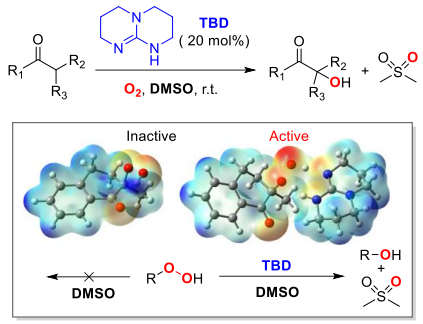

The dual catalytic role of TBD was revealed for the aerobic α-hydroxylation of ketones under a metal- and phosphine-free method. Via the doubly proton transfer process, TBD effectively activated the α-C(sp^3)-H bond of ketones, avoiding the necessity of alkali metal. Most importantly, TBD enhanced the activity of peroxide intermediate through the double hydrogen bonds, allowing its reduction by DMSO in absence of phosphine reductants.